

Remarks

I. Status

Claims 1-74 have been examined.

II. The Rejection Of Claims 1-74 As Obvious (Pursuant To 35 U.S.C. §§ 102(e)/103(a)) In Light Of Reddy *et al.* (U.S. Patent No. 5,648,213) taken in combination with Garman *et al.* (U.S. Patent No. 5,441,867)

The Examiner has rejected claims 1-74 as obvious (pursuant to 35 U.S.C. §§ 102(e)/103(a)) in light of Reddy *et al.* (U.S. Patent No. 5,648,213) taken in combination with Garman *et al.* (U.S. Patent No. 5,441,867). The cited Reddy *et al.* patent is stated to teach a method of producing an oligonucleotide-protein conjugate that includes reacting an oligonucleotide containing an amine group with a thiol group of a protein. The reaction is stated to employ a heterobifunctional reagent having a first reactive group that is specific for the amine group of the oligonucleotide, and a second reactive group that is specific for the thiol group of the protein. The cited Garman *et al.* patent is stated to establish that thiol containing proteins having either native or introduced thiol groups can be coupled to oligonucleotides using conventional heterobifunctional linkers.

Applicants respectfully traverse the rejection and request reconsideration. Applicants respectfully invite the Examiner's further review of the cited Garman *et al.* patent. Applicants note the Examiner's conclusion as to the teaching of the cited Garman *et al.* patent. However, Applicants' review of the reference has not uncovered any teaching or suggestion that a *thiolated protein* may be coupled to *an oligonucleotide*.

Applicants respectfully submit that the cited Garman *et al.* reference concerns the production of a "pre-activated" *protein* that would be capable of conjugating with thiol-containing *oligonucleotides* and *proteins*. In this regard, Applicants respectfully draw the Examiner's attention to column 2, lines 25-28, which read as follows:

"...*the protein* is chemically modified for covalent coupling to a thiol group of a thiolated *polynucleotide* or to a thiol group of a *thiol containing protein*." [Emphasis added]

The Examiner's attention is further directed to column 5, lines 50-54, where, again, Garman *et al.* discuss only the ability of a thiol-containing *protein* to couple to a thiol-reactive *protein*:

"Therefore according to a further aspect of the present invention we provide a stable lyophilised protein reagent pre-activated for covalent coupling to a thiol group of a thiolated *polynucleotide* or to a thiol group of a *thiol containing protein*. [Emphasis added]"

It is accordingly submitted that, contrary to the expressed conclusion of the Examiner, the cited Garman *et al.* patent teaches only that a thiol containing protein can be coupled to *another protein molecule*.

It is therefore respectfully submitted that the cited Garman *et al.* reference fails to contemplate the possibility that a thiol-containing *protein* could be conjugated to a thiol-reactive *oligonucleotide*. It is further submitted that in light of this failing, those of ordinary skill would not have considered the present invention to have been obvious in light of the combined teachings of the cited Reddy *et al.* and Garman *et al.* patents or of either reference alone.

As discussed in the present specification, by modifying the *oligonucleotide* to possess an *amino group* and conjugating a thiol-containing protein to that group (as described in more detail in the present specification) the present invention provides higher yields than are attainable using thiolated oligonucleotides (please see pages 9-10 of the present specification). This enhancement is not suggested by the cited prior art.


Accordingly, Applicants submit that the rejection of claims 1-74 as obvious (pursuant to 35 U.S.C. §§ 102(e)/103(a)) in light of Reddy *et al.* (U.S. Patent No. 5,648,213) taken in combination with Garman *et al.* (U.S. Patent No. 5,441,867) may be properly withdrawn.

Having now fully responded to all of the Examiner's rejections, Applicants respectfully submit that the present application is in condition for Allowance, and earnestly solicit early notice of such favorable action. The Examiner is respectfully

requested to contact the undersigned with respect to any issues regarding this application.

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Respectfully Submitted,


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